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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/788,188 | 02/16/2001 | Mark Tuszynski | 041673/2045 | 5329 |

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| EXAMINER | |
|---|---|
| CHEN, SHIN LIN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 05/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/788,188 | TUSZYNSKI ET AL. | |
| | Examiner | Art Unit | |
| | Shin-Lin Chen | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-6 and 8-25* is/are pending in the application.

4a) Of the above claim(s) *11-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-11-05 has been entered.

Applicants' amendment filed 4-11-05 has been entered. Claim 9 has been amended. Claims 1, 2, 4-6 and 8-25 are pending. Claims 1, 2, 4-6 and 8-10 and SEQ ID No. 2 are under consideration.

### *Election/Restrictions*

As discussed in the Official final rejection mailed 3-10-04, the restriction requirement is still deemed proper and remains FINAL.

This application contains claims 11-25 drawn to an invention nonelected with traverse in Paper Nos. 13 and 16. **A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action** (37 CFR 1.144) See MPEP § 821.01. Applicants' amendment filed 4-11-05 only states withdrawal of claims 11-25, however, cancellation of the non-elected claims 11-25 is required.

### *Specification*

2. The disclosure is objected to because of the following informalities: The specification states "a chart comparing the BDNF, hNGF and NT-3 coding sequences is provided in Figure 2" on page 3 first paragraph. However, there is no figure in the instant application.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 2, 4-6 and 8-10 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims encompass naturally occurring mutant pro-neurotrophin, which are not considered patentable subject matter. See MPEP 2105. This rejection could be overcome by amending the claims to recite "an isolated mutant pro-neurotrophin".

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 2, 4-6, 8 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "NGF", "NT-3" and "BDNF" in claim 1 are vague and render the claim indefinite. The terms "NGF", "NT-3" and "BDNF" are abbreviations which can stand for various meanings. Spelling out the terms would be remedial. Claims 2 and 4 depend from claim 1 but fail to clarify the indefiniteness.

The term "NT 4/5" in claim 5 is vague and render the claim indefinite. The term "NT 4/5" is an abbreviation which can stand for various meanings. Spelling out the term would be remedial. Claims 6, 8 and 10 depend from claim 5 but fail to clarify the indefiniteness.

### *Claim Rejections - 35 USC § 112*

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2, 4-6, 8 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 4-6, 8 and 10 read on a mutant pro-neurotrophin, such as NGF, NT-3, BDNF and NT 4/5, having an asparagine residue at a position 8 amino acids or at a position 4 amino acids upstream of the cleavage site for the mature neurotrophin substituted with a basic residue, such as serine. The specification discloses wild type human NGF, BDNF, NT-3 and NT-4/5 amino acid sequences (SEQ ID Nos. 1, 3, 5, 7) and mutant pro-neurotrophin amino acid

sequences of human NGF, BDNF, NT-3 and NT-4/5 (SEQ ID Nos. 2, 4, 6, 8). SEQ ID Nos. 2, 4 and 6 have asparagine at a position 8 amino acids upstream of cleavage site of mature neurotrophin substituted with serine and SEQ ID No. 8 has asparagine at a position 5 **(not 4)** amino acids upstream of cleavage site of mature growth factor substituted with serine.

The claims encompass any mutant pro-neurotrophin of NGF, NT-3, BDNF or NT 4/5 derived from numerous different organisms, such as humans, mice, rats, cats, dogs, bovines, ovines, birds, other mammals, fishes, and insects etc. NGF includes alpha-NGF, beta-NGF and gamma-NGF. The specification fails to provide sufficient description for the cleavage site of numerous mature neurotrophin family members and whether either at a position 8 amino acids or 4 amino acids upstream of said cleavage site would be an asparagine that can be substituted with a basic residues, such as serine. Although the claims limit the mutated position to 8 or 4 amino acids upstream of cleavage site, however, the scope of the claimed mutant neurotrophin is very broad and there is the lack of description of the cleavage site of various different neurotrophin family members derived from numerous organisms. The state of the art reveals that the NGF propeptide contains one tetrabasic and two dibasic cleavage sites (see Heymach Jr. et al., 1996, The Journal of Biological Chemistry, Vol. 271, No. 41, pp. 25430-25437, IDS-A21, page 25433, right column). It is unclear whether position 8 or 4 amino acid residues upstream of the different cleavage sites of the human NGF would be asparagines that can be substituted with serine. It is also unclear whether position 8 or 4 amino acid residues upstream of the cleavage sites of different neurotrophin derived from various organisms would be asparagines that can be substituted with serine. The specification only discloses the sequences of human NGF, NT-3, BDNF and NT 4/5. The genus of various pro-neurotrophin mutant is highly variant because a

significant number of structural differences between genus members is permitted. The specification fails to provide the structural features of the cleavage site of various different neurotrophin family members and their upstream amino acid sequences. The specification also fails to provide sufficient description for whether there is an asparagine residue at position 4 or 8 amino acid residues upstream of the cleavage site of mature NGF, NT-3, BDNF and NT 4/5 derived from various organisms.

This limited information disclosed by the present application is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed mutant pro-neurotrophin proteins. Thus, it is concluded that the written description requirement is not satisfied for the mutant pro-neurotrophin proteins as claimed.

Applicants cite specification page 2, line 28 through page 3, line 11 and argue that those neurotrophin molecules are higly homologous including the glycosylation site of the pro-pro region and the structure of the cleavage sites are pre-pro regions is specifically identifyied in SEQ ID Nos. 1-6 (amendment, p. 7). This is not found persuasive because of the reasons set forth above. The specification only discloses that the pre-neurotrophin coding sequences share a remarkable degree of homology but fails to specify whether the position 8 or 4 amino acid residue upstream of a cleavage site would be an asparagines that can be substituted to a basic residue. The specification only discloses the sequences of human NGF, NT-3, BDNF and NT 4/5. The claims encompass any mutant pro-neurotrophin of NGF, NT-3, BDNF or NT 4/5 derived from numerous different organisms, such as humans, mice, rats, cats, dogs, bovines, ovines, birds, other mammals, fishes, and insects etc. NGF includes alpha-NGF, beta-NGF and gamma-NGF. The specification fails to provide sufficient description for the cleavage site of

numerous mature neurotrophin family members and whether either at a position 8 amino acids or 4 amino acids upstream of said cleavage site would be an asparagine that can be substituted with a basic residues, such as serine.

8. Claims 1, 2, 4-6, 8 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the amino acid sequence comprising SEQ ID No. 2, does not reasonably provide enablement for any mutant pro-neurotrophin having an asparagine residue at a position 8 amino acids or at a position 4 amino acids upstream of the cleavage site for the mature neurotrophin substituted with a basic residue, such as serine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 2, 4-6, 8 and 10 read on a mutant pro-neurotrophin, such as NGF, NT-3, BDNF and NT 4/5, having an asparagine residue at a position 8 amino acids or at a position 4 amino acids upstream of the cleavage site for the mature neurotrophin substituted with a basic residue, such as serine. Claims 2 and 6 specify the basic residue is serine. Claims 4 and 8 specify the mutant pro-neurotrophin is a recombinant protein. Claim 10 specifies the mutant pro-neurotrophin comprises the precursor polypeptide of claim 5 joined by a cleavage site to a corresponding mature neurotrophin.

The specification discloses wild type human NGF, BDNF, NT-3 and NT-4/5 amino acid sequences (SEQ ID Nos. 1, 3, 5, 7) and mutant pro-neurotrophin amino acid sequences of human NGF, BDNF, NT-3 and NT-4/5 (SEQ ID Nos. 2, 4, 6, 8). SEQ ID Nos. 2, 4 and 6 have asparagine at a position 8 amino acids upstream of cleavage site of mature growth factor

substituted with serine and SEQ ID No. 8 has asparagine at a position 5 (**not 4)** amino acids upstream of cleavage site of mature growth factor substituted with serine.

The claims encompass any mutant pro-neurotrophin of NGF, NT-3, BDNF or NT 4/5 derived from numerous different organisms, such as humans, mice, rats, cats, dogs, bovines, ovines, birds, other mammals, fishes, and insects etc. NGF includes alpha-NGF, beta-NGF and gamma-NGF. The specification fails to provide sufficient description for the cleavage site of numerous mature neurotrophin family members and whether either at a position 8 amino acids or 4 amino acids upstream of said cleavage site would be an asparagine that can be substituted with a basic residues, such as serine. As discussed above under 35 U.S.C. 112 first paragraph written description rejection, the limited information disclosed by the present application is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed mutant pro-neurotrophin proteins. Thus, one skilled in the art at the time of the invention would not know how to use the claimed mutant neurotrophin proteins.

The specification fails to provide adequate guidance and evidence for whether a mutant neurotrophin protein, other than SEQ ID No. 2, having an asparagine residue at a position 8 amino acid or at a position 4 amino acid upstream of the cleavage site for the mature neurotrophin substituted with a basic residue, such as serine, would have improved secretion efficiency from host cells than wild-type neurotrophin. The specification also fails to provide the structural features of the cleavage site of various different neurotrophin derived from numerous organisms and their upstream amino acid sequences. It should be noted that the amino acid residue at a position 4 amino acids upstream of the cleavage site of NT4/5 is arginine (R) not asparagine (N). The specification fails to provide adequate guidance and evidence for whether

substitution of the amino acid residues at a position 4 amino acids upstream of the cleavage site of any NGF, NT-3, BDNF, or NT 4/5 derived from various organisms with any basic residues, including serine, would result in mutant pro-neurotrophin having improved secretion efficiency from host cells than wild-type neurotrophin.

The specification states that "Despite many of their structural similarities, nervous system growth factors act on discrete and different targets. Little is known about which amino acid residues within a growth factor are necessary to its activity...as little as the first 9 residues of the N-terminus and the last two residues from the C-terminal of purified recombinant human NGF produces a neurotrophin molecule which is 300-fold less efficient in binding activity as compared to wild-type hNGF" (specification, p. 3, lines 5-11). Further, the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title).

Further, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of

proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Heymach Jr. et al., 1996 (The Journal of Biological Chemistry, Vol. 271, No. 41, pp. 25430-25437, IDS-A21) reports that when mutant NGF precursors having mutation at the N-glycosylation site (N(-8)G, N(-53)Q and N(-8, -53)Q) are expressed in COS cells, mature and biologically active NGF protein was secreted at lower levels than wild-type NGF (e.g. p. 25434, right column, Figure 4). The result shown by Heymach is to the contrary of the present invention. In addition, NGF, NT-3, BDNF and NT 4/5 are different neurotrophin proteins having different biological functions. NGF, NT-3, BDNF and NT 4/5 derived from different organisms are also different proteins having different amino acid sequences and distinctive biological functions. Since protein function was unpredictable at the time of the invention, a substitution of an asparagine with a basic residue in those neurotrophin precursor proteins could result in different effects on the function of said neurotrophin precursor proteins. Whether a substitution of an asparagine at position 8 or 4 amino acid residue upstream of a cleavage site with a basic residue in those neurotrophin precursor proteins would improve secretion efficiency was unpredictable and requires trial and error experimentation to determine the biological function of the mutant neurotrophin proteins and to determine whether the secretion efficiency is improved as compared to wild type protein.

In view of the scope of the claimed invention, the lack of structural features of the cleavage site of the neurotrophin precursor protein within its upstream amino acid sequence, and the unpredictability of protein function from mere amino acid sequence, one skilled in the art at the time of the invention would not know how to use the claimed mutant neurotrophin proteins.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the level of one of ordinary skill which is high, the amount of experimentation necessary, the working example provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicants argue that the substitution of asparagine for serine in the targeted N-glycosylation site is achievable and was shown in SEQ ID Nos. 1-6 (amendment, p. 7-8). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112, first paragraph, enablement rejection and claims 1, 4, 5, 8 and 10 also encompass substituting the asparagine residue with any basic residue other than serine.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Shin-Lin Chen, Ph.D.

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